## INTRODUCTION TO PRINCIPLES OF CLINICAL PHARMACOLOGY



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#### **COURSE MODULES**

**MODULE 1: PHARMACOKINETICS** 

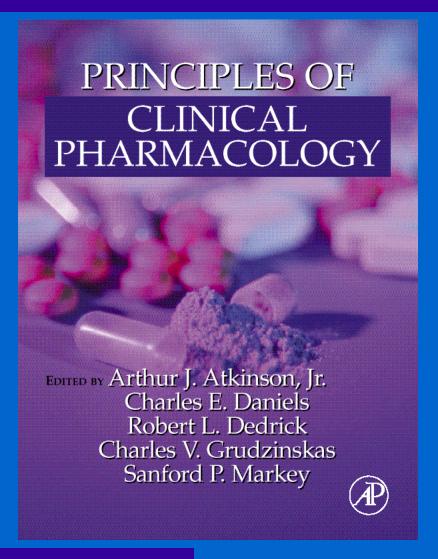
**MODULE 2: DRUG METABOLISM & TRANSPORT** 

**MODULE 3: ASSESSMENT OF DRUG EFFECTS** 

MODULE 4: OPTIMIZING & EVALUATING PATIENT THERAPY

**MODULE 5: DRUG DISCOVERY & DEVELOPMENT** 

#### REQUIRED TEXT



#### THE WARREN GRANT MAGUSON CLINICAL CENTER OF THE NATIONAL INSTITUTES OF HEALTH

PRESENTS THIS CERTIFICATE TO

### John B. Smith, M.D.

IN RECOGNITION OF PARTICIPATION IN THE

## NIH CLINICAL CENTER COURSE IN Principles of Clinical Pharmacology

September 5, 2002 through April 24, 2003

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#### **CLINICAL PHARMACOLOGY**

## THE STUDY OF DRUGS IN HUMANS

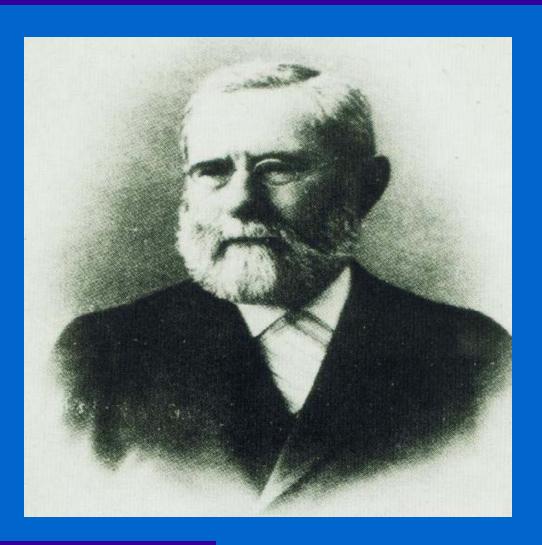
#### CAREER GOALS OF CLINICAL PHARMACOLOGISTS

- OPTIMIZE UNDERSTANDING AND USE OF EXISTING MEDICINES
- DEVELOP NEW MEDICINES

#### **JOHN JACOB ABEL** 1857 - 1938



#### OSWALD SCHMIEDEBERG 1838 - 1921



#### RUDOLPH BUCHEIM 1820 - 1879



## LACK OF IMPORTANCE ATTACHED TO DRUG THERAPY

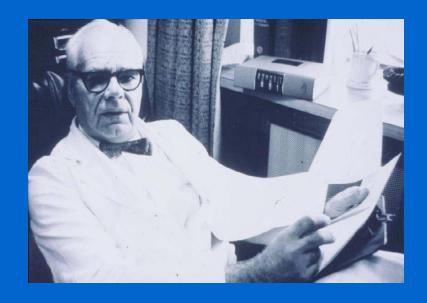
"FORTUNATELY A SURGEON WHO USES THE WRONG SIDE OF THE SCALPEL CUTS HIS OWN FINGERS AND NOT THE PATIENT; IF THE SAME APPLIED TO DRUGS THEY WOULD HAVE BEEN INVESTIGATED VERY CAREFULLY A LONG TIME AGO."

Rudolph Bucheim Beitrage zur Arzneimittellehre, 1849

#### FOUNDERS OF AMERICAN CLINICAL PHARMACOLOGY



**HARRY GOLD** 



WALTER MODELL

## PARTIAL LIST OF GOLD AND MODELL ACCOMPLISHMENTS

- 1937 INTRODUCED DOUBLE-BLIND TRIAL DESIGN \*
- 1939 INITIATED CORNELL CONFERENCES ON THERAPY
- 1953 ANALYZED DIGOXIN EFFECT KINETICS TO ESTIMATE ABSOLUTE BIOAVAILABILITY AS WELL AS TIME-COURSE OF CHRONOTROPIC EFFECTS †
- 1960 FOUNDED CLINICAL PHARMACOLOGY AND THERAPEUTICS
  - \* Gold H, Kwit NT, Otto H. JAMA 1937;108:2173-2179.
  - † Gold H, Cattell McK, Greiner T, Hanlon LW, Kwit NT, Modell W, Cotlove E, Benton J, Otto HL. J Pharmacol Exp Ther 1953:109;45-57.

#### LINEAGE OF MODERN CLINICAL PHARMACOLOGY

PATER FAMILIAS

**RUDOLPH BUCHEIM** 

FOUNDING FATHERS

US

**HARRY GOLD** 

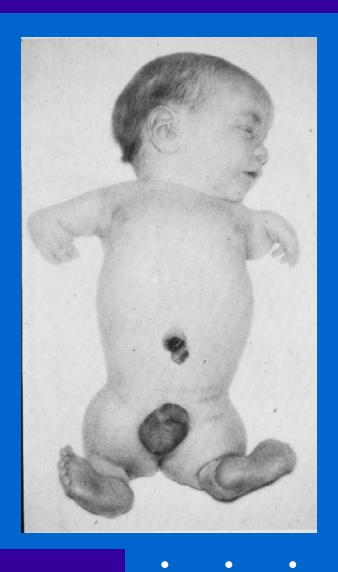
WALTER MODELL

**EUROPE** 

**PAUL MARTINI** 

#### **THALIDOMIDE**

#### **PHOCOMELIA**



#### SERIOUS ADR

A SERIOUS ADVERSE DRUG REACTION
IS AN ADVERSE DRUG REACTION
THAT REQUIRES OR PROLONGS
HOSPITALIZATION, IS PERMANENTLY
DISABLING OR RESULTS IN DEATH

#### CONSEQUENCES OF THALIDOMIDE CRISIS

- NEW FDA REGULATIONS (KEFAUVER-HARRIS 1962 AMENDMENTS)
- IOM-NAS REVIEW OF THERAPEUTIC CLAIMS
- † INVESTIGATION OF ADR CAUSES
- NIGMS FUNDING FOR 10 CLINICAL PHARMACOLOGY CENTERS

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FOUNDING FATHERS

<u>US</u>

HARRY GOLD

WALTER MODELL

**EUROPE** 

**PAUL MARTINI** 

#### RENAISSANCE LEADERS

US

KEN MELMON LEON GOLDBEG JAN KOCH-WESER JOHN OATES
DAN AZARNOFF
LOU LASAGNA

**EUROPE** FOLKE SJŐQVIST

**COLLIN DOLLERY** 

#### FACTORS CONTRIBUTING TO ADR'S

- 1. INAPPROPRIATE POLYPHARMACY
- 2. LACK OF CLEAR THERAPEUTIC GOALS
- 3. FAILURE TO ATTRIBUTE NEW SYMPTOMS OR LABORATORY TEST RESULTS TO THERAPY
- 4. LOW PRIORITY GIVEN TO STUDYING ADR'S
- 5. GENERAL IGNORANCE OF PHARMACOLOGY

#### ADVERSE DRUG REACTIONS

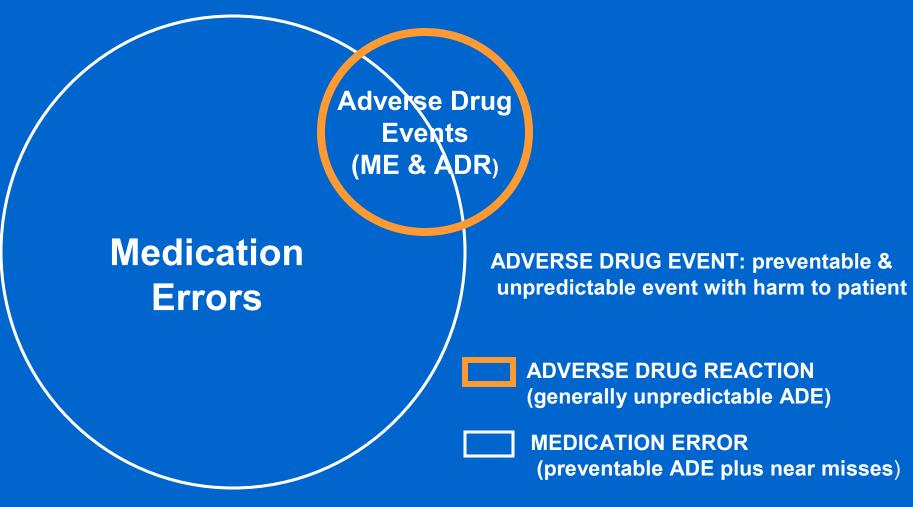
WHO:

ANY UNTOWARD REACTION TO A DRUG

**CONTEMPORARY VIEW:** 

UNPREDICTABLE ADVERSE DRUG EVENTS

#### **ADVERSE DRUG EVENTS\***



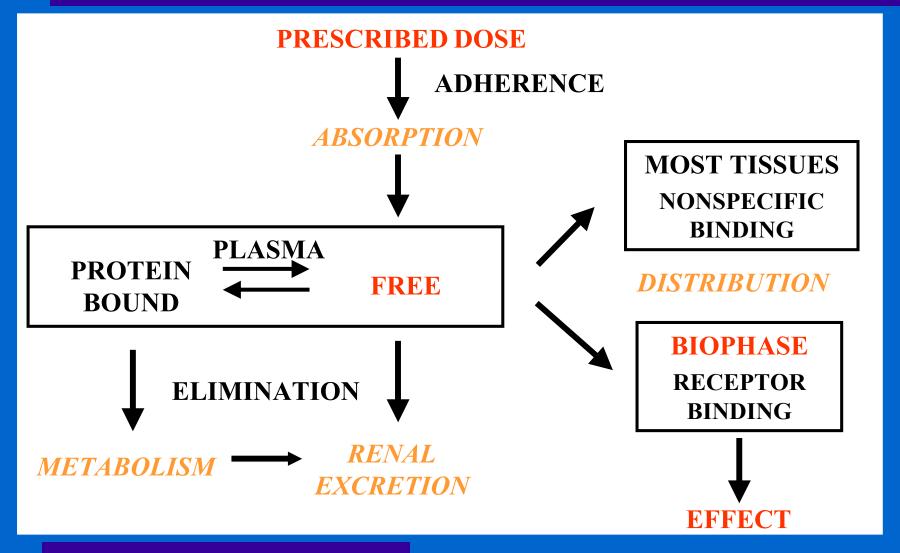
\* From Bates DW, et al. J Gen Intern Med 1995;10:199-205.

#### **CHARACTERISTICS OF MOST ADRs\***

- MOST <u>NOT</u> CAUSED BY NEW DRUGS
- MOST <u>NOT</u> IDIOSYNCRATIC REACTIONS
- ~80% <u>ARE</u> RELATED TO DRUG DOSE

\* Melmon KL. N Engl J Med 1971;284:1361-8.

#### RATIONALE FOR PLASMA LEVEL MONITORING



#### **NONCANCER DRUGS CAUSING ADR'S\***

PHENYTOIN\*\*

CARBAMAZEPINE\*\*

PREDNISONE CODEINE

DIGOXIN\*\*

LITHIUM\*\*

AMIODARONE THEOPHYLLINE\*\*

ASPIRIN\*\*

DESIPRAMINE\*\*

CO-TRIMOXAZOLE DEXAMETHASONE

PENTAMIDINE GENTAMICIN\*\*

\* 1988 NMH DATA (CLIN PHARMACOL THER 1996;60:363-7)

\*\* DRUGS FOR WHICH PLASMA LEVELS ARE AVAILABLE

#### **INCIDENCE OF ADRS**\*

#### IN HOSPITALIZED PATIENTS

ALL SEVERITIES	10.9%
SERIOUS	2.1%
FATAL	0.19%

## AS CAUSE OF HOSPITAL ADMISSION SERIOUS 4.7%

FATAL 0.13%

<sup>\*</sup> Lazarou J, et al. JAMA 1998;279:1200-05.

## ATTENTION FOCUSED ON MEDICAL ERRORS

## "TO ERR IS HUMAN BUILDING A SAFER HEALTH SYSTEM"

Committee on Quality of Health Care in America Institute of Medicine

www.nap.edu/reading room.

#### CAREER GOALS OF CLINICAL PHARMACOLOGISTS

- OPTIMIZE UNDERSTANDING AND USE OF EXISTING MEDICINES
- DEVELOP NEW MEDICINES

## MEDICINES "DISCOVERED" BY CLINICAL INVESTIGATORS

**NEW INDICATION:** 

**ALLOPURINOL (GOUT) - RW RUNDLES** 

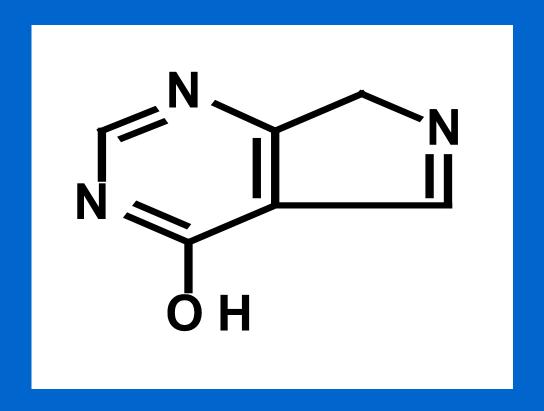
**ENDOGENOUS COMPOUND:** 

**DOPAMINE (SHOCK) - LI GOLDBERG** 

**DRUG METABOLITE:** 

FEXOFENADINE (ANTIHISTAMINE) - RL WOOSLEY ET AL.

#### **ALLOPURINOL\***



\* Rundles RW, Metz EN, Silberman HR. Ann Intern Med 1966;64:229-57.

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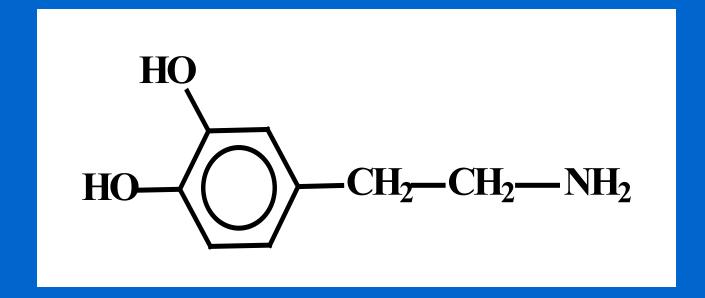
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#### **DOPAMINE\***



\*Goldberg LI. Pharmacol Rev 1972;24:1-29.

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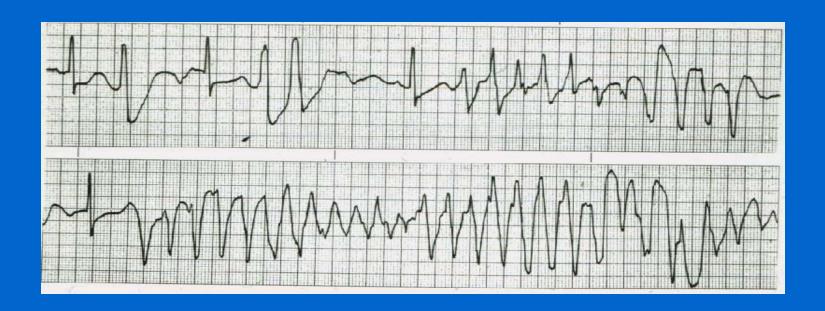
**ENDOGENOUS COMPOUND:** 

**DOPAMINE (SHOCK) - LI GOLDBERG** 

**DRUG METABOLITE:** 

FEXOFENADINE (ANTIHISTAMINE) - RL WOOSLEY ET AL.

#### TORSADES DE POINTES



#### TERFENADINE METABOLISM\*

HO-C-N-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH-C-CH<sub>3</sub>

$$CH_3$$

$$CH$$

**TERFENADINE** 

TERFENADINE CARBOXYLATE

\* From Woosley RL, et al. JAMA 1993;269:1532-6.

#### **PHARMACOKINETICS**

# THE QUANTITATIVE ANALYSIS OF THE TIME COURSE OF DRUG ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

#### **PHARMACOKINETICS**

## BECAUSE IT IS QUANTITATIVE, PHARMACOKINETICS IS INESCAPABLY MATHEMATICAL

#### ROLE OF RIGHT TRIANGLES IN PYRAMID DESIGN



#### SOME RIGHT TRIANGLES

THE FOLLOWING DIMENSIONS CAN BE MEMORIZED TO HELP CONSTRUCT RIGHT TRIANGLES:

3, 4, 5

5, 12, 13

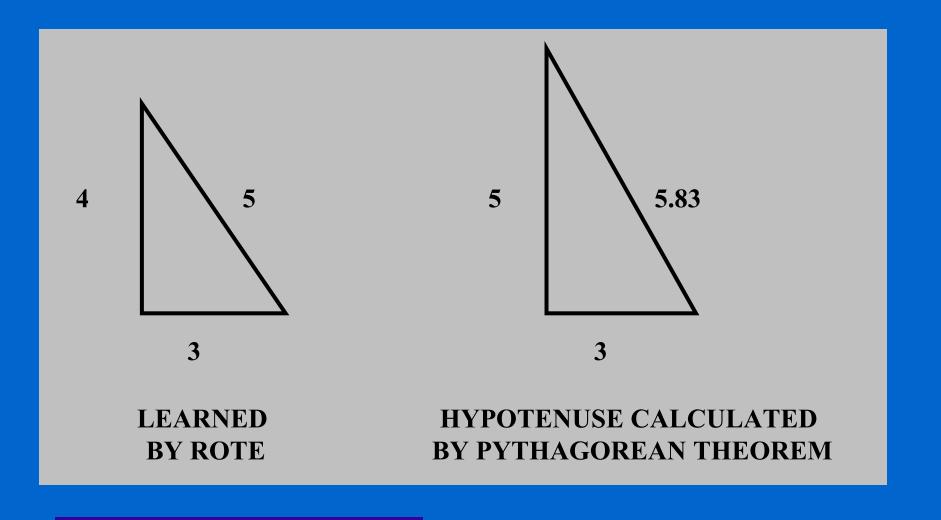
8, 15, 17

7, 24, 25

# INCREASING SOPHISTICATION IN ARCHITECTURE AND MATH



#### CONSTRUCTION OF RIGHT TRIANGLES



#### CREATININE CLEARANCE EQUATION

$$CL_{Cr} = \frac{U \times V}{P}$$

**U** = **URINE CONCENTRATION** 

V = URINE VOLUME

P = PLASMA CONCENTRATION

#### CREATININE CLEARANCE REVISTED

RATE OF APPEARANCE OF Cr IN URINE (dE/dt):

 $dE/dt = CL_{Cr} \times P$ 

RATE OF CHANGE OF Cr IN BODY (dX/dt):

 $dX/dt = -CL_{Cr} \times P$ 

AT STEADY STATE:

 $P = I / CL_{Cr}$ 

I = RATE OF CREATININE SYNTHESIS

#### STEADY STATE CONCENTRATION

#### **CONTINUOUS CREATININE SYNTHESIS:**

$$C_{SS} = \frac{I}{CL_{Cr}}$$

#### **CONTINUOUS DRUG INFUSION:**

$$C_{SS} = \frac{I}{CL_{E}}$$

#### COCKCROFT & GAULT EQUATION\*

$$CL_{Cr} = \frac{(140 - age) (weight in kg)}{72 (serum Cr in mg/dL)}$$
[reduce estimate by 15% for women]

\* Cockroft DW, Gault MH: Nephron 1976;16:31-41.

#### **COCKCROFT & GAULT EQUATION**

$$CL_{Cr} = \frac{I}{P}$$

$$CL_{Cr} = \frac{(140 - age) \text{ (weight in kg)}}{}$$

72 (serum Cr in mg/dL)

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.

## RENAL FUNCTION IN PATIENTS TOXIC FROM DIGOXN\*

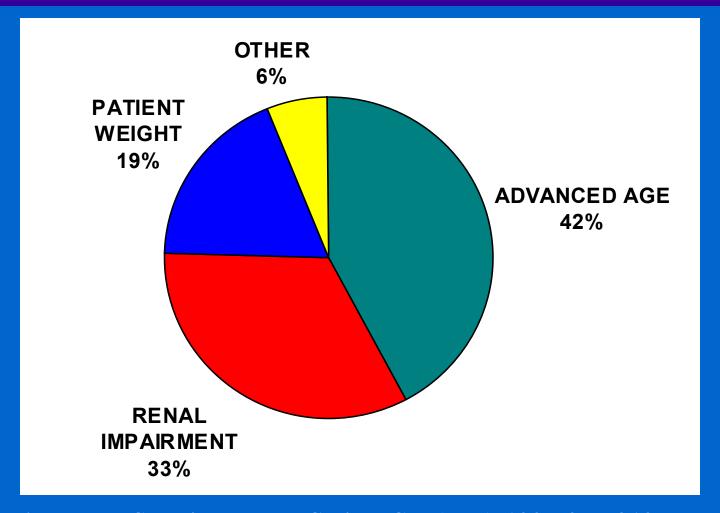
SERUM	Cl <sub>Cr</sub> (mL/min)		
Cr	≥ 50	< 50	
<b>≤</b> 1.7	4	19	52%
> 1.7	0	21	48%

<sup>\*</sup> From Piergies AA, et al. Clin Pharmacol Ther 1994;55:353-8.

### ESTIMATED Cl<sub>Cr</sub>

- ESSENTIAL FOR SAFE & EFFECTIVE USE OF RENALLY ELIMINATED DRUGS
- IMPORTANT PREREQUISITE FOR APPLICATION OF PK PRINCIPLES
- NEED TO AUTOMATE BUT:
  - LAB SYSTEM OFTEN DOESN'T "TALK" WITH PATIENT DATA BASE
  - PATIENTS OFTEN NOT WEIGHED

### PATHOPHYSIOLOGIC FACTORS NOT ACCOUNTED FOR IN DRUG DOSING\*



<sup>\*</sup> Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.